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AMPICILLIN BY INJECTION AND BY MOUTH IN THE TREATMENT OF ACUTE GONORRHOEA*

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Ampicillin ("Penbritin") has been shown to be active against the gonococcus both when used by mouth (Willcox, 1963, 1964; Alergant, 1963) and *in vitro* (Ödegaard, 1962). Little or no published data are so far available concerning the use of the injectable sodium salt of ampicillin, which is supplied in vials in the form of a white powder in amounts equivalent to 250 or 500 mg. ampicillin. It is dissolved in 1·5 ml. distilled water before use by intramuscular injection and is well tolerated. The made-up solution is, however, unstable and should be used immediately.

The present paper reports the results of treating 81 male patients with acute uncomplicated gonorrhoea with single injections of 250 or 500 mg. ampicillin, and contrasts them with the results in 250 cases in which various oral dosages of ampicillin were used and in 279 others who received single injections of 1·2 mega units aqueous procaine penicillin.

Ampicillin by Injection

Material

81 male patients with uncomplicated gonorrhoea were treated with intramuscular injections of ampicillin. Of these 44 were Negroes (38 from the West Indies, three from West Africa, two from Fiji, and one from the USA), nineteen were from the United Kingdom, four were from India, two each from Italy, Eire, Pakistan, and Spain, and one each from Brazil, Canada, Cyprus, Holland, Malta, and Spain. The average age was 27 years. Fourteen were married and 67 were single.

38 patients had had no previous venereal infection although one of these had had a mumps orchitis; the remaining 43 had had between them no less than 149 previous attacks of gonorrhoea, thirty of non-gonococcal urethritis, two of syphilis, two of balanitis, one of lymphogranuloma venereum, one of penile sore, one of penile lymphangitis, and one of anxiety concerning venereal disease. No less than 159 of the 187 previous incidents had affected the Negro patients who thus had been involved in an average of 3·6 previous incidents each, compared with 0·8 each for the remainder.

The discharge had been present for 1 to 3 days in 52 cases, 4 to 7 days in 26, 8 to 14 days in two, and for longer than this time in one case. 68 patients complained of some dysuria and thirteen did not. The disease was stated to have been caught from a female stranger in 49 instances, from a friend or acquaintance in 31, and from a male in one case. The apparent incubation period was 1 to 3 days in 38 cases, 4 to 7 days in 34, 8 to 14 days in five, 15 to 21 days in one, 20 to 28 days in one, and over one month in one: in one case it was unknown.

Routine Wassermann reactions and VDRL (or Kahn) tests were both negative in all but one West Indian patient in whom a weakly positive Wassermann reaction but a negative Kahn test were reported.

Management

Gonococci were found in Gram-stained urethral smears in all cases before treatment; routine serum tests for syphilis were also carried out. All patients received sodium ampicillin intramuscularly; fifty had 250 mg. and 31 had 500 mg. in single injections. It was intended to see the patients subsequently at approximately 3, 7, 14, 28, 56, and 84 days following treatment for an examination of the urethra for discharge (a smear being taken if a discharge was present) and of the urine for haze and threads. It was intended to make at least one examination of the prostatic secretion during surveillance and to perform final serum tests for syphilis at 3 months. Not all the patients attended at the times requested but

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sufficient time elapsed for all to have been observed for at least one month from treatment.

No adverse side-effects were reported from the injectable preparation apart from one patient who stated he had seen his own doctor with a rash suspected as being due to penicillin; no complaints were received of pain from the injection.

Results

Single Dose of 250 mg.—The follow-up and results obtained are shown in Table I.

TABLE I

FOLLOW-UP AND RESULTS WITH SINGLE INJECTIONS OF 250 mg. AMPICILLIN

Follow-up (days)	No. Followed	No. Satis-factory	Non-gono-coccal Urethritis	Re-infections	Fail-ures
0	50	—	—	—	—
1–3	39	9	—	—	5
4–7	25	5	3	—	4
8–14	13	2	—	1	1
15–21	9	1	—	—	1
22–28	7	—	—	1	—
1–2 mths	6	2	1	2	1
2–3 mths	—	—	—	—	—
Total ..	39	19	4	4	12

Of 81 patients treated, 39 were followed. The status of nineteen of these at the last visit was satisfactory, four were treated for a non-gonococcal infection, four with a history of further exposure were treated for re-infection, and twelve were regarded as failures (30·8 per cent. of those followed), gonococci being found in the smears of all.

No satisfactory criteria exist to distinguish relapse from re-infection apart from the presence or absence of a history of further sexual exposure which is used in the Table presented.

Single Injection of 500 mg.—The follow-up and results of those given a single injection of 500 mg. are summarized in Table II.

TABLE II

FOLLOW-UP AND RESULTS OF PATIENTS TREATED WITH 500 mg. AMPICILLIN

Follow-up (days)	No. Followed	No. Satis-factory	Non-gono-coccal Urethritis	Re-infections	Fail-ures
0	31	—	—	—	—
1–3	24	—	—	—	2
4–7	22	3	1	—	4
8–14	14	3	—	—	1
15–21	10	2	—	1	—
22–28	7	—	1	—	—
1–2 mths	6	—	3	—	—
2–3 mths	3	1	—	—	—
Over 3 mths	2	—	—	2	—
Total ..	24	9	5	3	7

Of 31 treated, 24 were followed and there were seven suspected failures (29·2 per cent. of those followed).

Difficulties in distinguishing Relapse from Re-infection

One of the great difficulties in assessing the results of therapeutic agents in the treatment of gonorrhoea is that of deciding whether to classify an apparent treatment failure as a relapse or a re-infection. The latter has become an increasing possibility in recent years as gonorrhoea has again become more common.

The only readily available criterion of re-infection is a history of further sexual exposure, although the opportunity to find *Neisseria* in the new consort is seldom offered. Even if the consort is examined, and can be shown to harbour the gonococcus, this still does not necessarily exclude the occurrence of a relapse in the male.

Theoretically, the incubation period of gonorrhoea being generally accepted as 1 to 14 days, all failures occurring within 2 weeks are potential relapses, and those occurring after this time are likely to be re-infections. Indeed, when cases requiring re-treatment are classified as failures or re-infections solely on this basis, there is a close agreement with a classification based on a history of further sexual exposure.

Recent unpublished work by Curtis and Wilkinson (1964) at the London Hospital, based on the sensitivity patterns of the gonococcus, has shed further light on this problem. These workers have found a marked difference in the sensitivity pattern of gonococci cultured from previously untreated cases and from cases requiring re-treatment following the use of penicillin; strains from failures occurring within a few days of treatment required much higher penicillin levels for inhibition. This trend was apparent in failures noted within 7 days of treatment, but in those noted after 7 days the sensitivity pattern was similar to that in previously untreated cases. These workers therefore consider that in practice the classification of all recurrences (irrespective of history) noted within 7 days as treatment failures and of those noted after 7 days as re-infections provides a fairly accurate general picture.

Such a classification will not, of course, necessarily apply to every individual case. For example, some patients with relapses may not report until the 8th to 14th day, although the relapse may have occurred earlier. These would tend to bias the sensitivity pattern of failures noted after one week towards the pattern of relapse.

Also some cases of re-infection may be due to female consorts who are themselves penicillin failures and whose organisms will therefore exhibit the pattern of relapse rather than that of the common pool. This is perhaps a more serious objection as it will influence the trend of sensitivities found in relapses during the first week. A counter-bias from re-infections with less sensitive organisms is not likely to occur during this time as the females concerned will have been cured and will thus have been unable to cause re-infection.

A counter-balance is, however, provided by those cases which fail despite a normal sensitivity pattern if a sufficiently strong concentration of penicillin does not reach the focus of infection; such failures may be noted within the first week or the patients may report after this time. Also, not all cultures are successful and a few patients re-treated for non-gonococcal urethritis may in fact be cases of recurrent gonorrhoea from which gonococci were not grown and for which no sensitivity pattern was obtained.

With all these limitations in mind, this approach may provide a useful method of assembling data for comparison provided that the data compared are obtained from the same city at the same time, a proviso which will lessen the influence of variations in gonococcal sensitivity to penicillin, which itself is no static phenomenon. The method suggested has therefore also been applied to the data given in this paper.

Results of Two Schedules compared

Three methods of comparison are used:

(*a*) Failures rather than re-infections are assessed on the basis of further sexual exposure;

(*b*) All recurrences in the first week are classified as failures, the failure rate being calculated as a percentage of those followed;

(*c*) The same as (*b*) with the failure rate calculated as a percentage of all those treated irrespective of follow-up (Table III).

TABLE III

RESULTS WITH 250 AND 500 mg. AMPICILLIN COMPARED

Dosage Schedule (mg.)	No. Treated	No. Followed	Failures	Per cent. Failed of those Followed	Recurrence in First Week		
					No.	Per cent. of No. Followed	Per cent. of No. Treated
250	50	39	12	30·8	9	23·1	18·0
500	31	24	7	29·2	6	25·0	19·4
Total	81	63	19	30·2	15	23·8	18·5

By all methods of comparison there was nothing to favour a single injection of 500 mg. rather than of 250 mg.

Results in Negro and other Patients

As the Negroes have clearly been shown to have had many more previous infections with gonorrhoea than the other patients, the possibilities of re-infection in this group are theoretically much higher. The results are classified by race in Table IV.

TABLE IV

RESULTS IN NEGRO PATIENTS AND OTHERS

Race	No. Treated	No. Followed	Failures	Per cent. Failed of those Followed	Recurrence in First Week		
					No.	Per cent. of No. Followed	Per cent. of No. Treated
Negro	44	35	8	22·9	6	17·1	13·6
Others	37	28	11	39·3	9	32·1	24·3
Total	81	63	19	30·2	15	23·8	18·5

There was nothing to suggest by any of the three methods of assessment that the results were worse in Negroes—indeed the opposite was the case.

Ampicillin by Mouth

250 males with acute gonorrhoea were treated with ampicillin by mouth; 100 received single doses of 500 mg., 100 received single doses of 750 to 1,000 mg., and fifty had two doses each of 1 g. at an interval of 5 to 6 hours. The series of cases has been described (Willcox, 1963). The case management was similar to that employed in the cases treated by injection. The follow-up and results obtained are shown in Table V.

TABLE V

AMPICILLIN BY MOUTH: FOLLOW-UP AND RESULTS

Follow-up (days)	No. Followed	No. Satisfactory	Non-gonococcal Urethritis	Re-infections	Failures
0	250	—	—	—	—
1–7	217	79	6	—	19
8–14	113	19	14	4	4
15–21	72	8	4	1	3
22–28	56	6	1	4	4
1–2 mths	41	13	3	6	1
2–3 mths	18	3	2	4	—
Over 3 mths	9	1	1	7	—
Total ..	217	129	31	26	31

Of 250 treated, 217 were followed and 31 (14·3 per cent. of those followed) were judged to be

TABLE VI

RESULTS OBTAINED WITH AMPICILLIN BY MOUTH

Dosage Schedule (mg.)	No. Treated	No. Followed	Suspected Relapses	Recurrence in First Week	Per cent. Relapse of those Followed	Per cent. Recurrence in First Week	
						Of No. Followed	Of No. Treated
500 single	100	84	12	7	14·3	8·3	7·0
750 single	50	44	7	4	15·9	9·1	8·0
1 g. single	50	46	7	7	15·2	15·2	14·0
Total Single	200	174	26	18	14·9	10·3	9·0
1 g.+1 g. double ..	50	43	5	1	11·6	2·3	2·0

failures. The failure rate was the same whatever the schedule.

When only the nineteen failures occurring within 7 days were counted, the failure rate was 8·8 per cent. of those followed or 7·6 per cent. of those treated. In this group, also, there was nothing to suggest higher failure rates in Negroes.

The results with single doses of 1 g. were no better than those with 500 or 750 mg. whatever the method of assessment. On the other hand, if double doses of ampicillin were given, the number of recurrences in the first week was significantly reduced (Table VI).

Aqueous Procaine Penicillin by Injection

A control group of male patients with uncomplicated acute gonorrhoea was treated with single injections of 1·2 mega units aqueous procaine penicillin under similar conditions during the same time as the ampicillin trials.

Of 279 patients treated, 207 were followed and there were 23 failures (11·1 per cent. of those followed) within 3 months. Only twelve of these failures occurred within the first week (5·8 per cent. of those followed or 4·3 per cent. of those treated). The results obtained with single injections of aqueous procaine penicillin by injection and with ampicillin in single doses by mouth and by injection are compared in Table VII. Using all three methods of assessment the results obtained with 250 to 500 mg. ampicillin by injection were only half as good as those obtained with single doses of 500 to 1,000 mg. ampicillin by mouth. The latter were somewhat less good than those obtained with single injections of 1·2 mega units (0·7 g.) aqueous procaine penicillin.

Summary and Conclusions

(1) 81 male patients with acute uncomplicated gonorrhoea were treated with a single intramuscular injection of ampicillin. Of fifty given 250 mg. there were twelve suspected relapses among 39 followed (30·8 per cent.). Of 31 given 500 mg. there were seven suspected failures among 24 followed (29·2 per cent.). The results were thus similar in the two groups.

(2) The results obtained with ampicillin by injection were only half as good as those obtained with single oral doses of 500 to 1,000 mg. ampicillin. Of 200 patients so treated, there were 26 suspected failures among 174 followed (14·9 per cent.). Again, as with the injections, the results obtained with single doses of 1 g. were not significantly better than those with 500 mg. When double oral doses, each of 1 g. given 5 to 6 hours apart, were used, there were five failures among 43 patients followed (11·6 per cent.).

(3) The results were compared with those in 279 cases treated with single injections of 1·2 mega units aqueous procaine penicillin; there were

TABLE VII

COMPARISON OF SINGLE DOSAGE METHODS

Dosage Schedule		No. Treated	No. Followed	Suspected Relapses	Recurrence in First Week	Per cent. Relapse of No. Followed	Per cent. Recurrence in First Week	
							Of No. Followed	Of No. Treated
Ampicillin	0·25–0·5 g. Single injection	81	63	19	15	30·2	23·8	18·5
	0·5–1·0 g. Single oral dose	200	174	26	18	14·9	10·3	9·0
Procaine penicillin	1·2 mega units (0·7 g.)	279	207	23	12	11·1	5·8	4·3

23 suspected relapses among 207 followed (11·1 per cent.).

(4) Difficulties in distinguishing between relapses and re-infections are discussed in the light of unpublished work at the London Hospital (Curtis and Wilkinson, 1964) which suggests that a fairly accurate distinction may be made if only those recurrences which occur in the first week are considered to be relapses. When this method of assessment was applied to the results of the present investigation, it showed a significant improvement if ampicillin was given in two oral doses; according to this method of classification, however, the success rates in the cases treated with procaine penicillin by injection were better than in those treated with ampicillin.

(5) It is concluded that, of the methods studied, 1·2 mega units aqueous procaine penicillin gives the best results in the treatment of acute gonorrhoea. Indifferent results may be obtained with single injections of 250 to 500 mg. ampicillin, but the failure rates so obtained can be halved by giving 500 to 1,000 mg. ampicillin in a single oral dose.

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L'ampicilline par voies intramusculaire et orale dans le traitement de la gonorrhée aigüe

RÉSUMÉ

(1) 81 patients mâles atteints de gonorrhée aigüe non compliquée furent traités par une seule piqûre intramusculaire d'ampicilline. Parmi les 50 qui reçurent 250 mg. d'ampicilline, sur 39 cas suivis 12 furent suspects de rechute (soit un pourcentage de rechute de 30,8%. Parmi les 31 qui reçurent 500 mg. d'ampicilline, sur 24 cas suivis 7 furent suspects de rechute (soit un pourcentage de rechute de 29,2%. Les résultats furent donc semblables dans les deux groupes.

(2) Mais les résultats obtenus en utilisant l'ampicilline par voie intramusculaire ne furent que deux fois moins bons que ceux obtenus en traitant par une seule dose orale de 500 à 1,000 mg. d'ampicilline. Parmi les 200 patients ainsi traités, sur 174 cas suivis, 26 furent suspects de rechute (soit un pourcentage de 14,9% de rechute). Une fois de plus, les résultats obtenus en traitant par une dose unique de 1 g. ne furent pas meilleurs que ceux obtenus en traitant par une dose unique de 500 mg. Quand on donna deux doses orales de 1 g. à 5 ou 6 h. d'intervalle, il y eut 5 échecs parmi les 43 malades suivis (soit 11,6% de rechute).

(3) On compara ces résultats avec ceux obtenus dans 279 cas traités par une seule piqûre de 1,2 méga-unité de procaine pénicilline en solution aqueuse; il y eut 23 rechutes parmi les 207 cas suivis (soit 11,1% de rechute).

(4) On discuta le diagnostic entre rechute et réinfection à l'aide de travaux non publiés, faits au "London Hospital" (Curtis et Wilkinson, 1964) qui suggèrent qu'un diagnostic différentiel exact est possible, en ne definissant comme rechutes que les cas survenant pendant la première semaine. Lorsque cette définition fut appliquée à l'investigation présente on trouva que les résultats les meilleurs étaient obtenus en traitant par deux doses buccales d'ampicilline. Cependant, selon cette classification, les résultats furent meilleurs dans le traitement par piqûre de procaine pénicilline que dans le traitement par ampicilline.

(5) En conclusion, des différentes méthodes étudiées, la meilleure pour traiter la gonorrhée aigüe est celle utilisant 1,2 méga unité de procaine pénicilline. Les résultats sont identiques, qu'on utilise 250 ou 500 mg. d'ampicilline par piqûre intramusculaire, mais peuvent être améliorés deux fois en donnant en plus 500 à 1000 mg. d'ampicilline en une seule dose orale.